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Provisional Peer Reviewed Toxicity Values for delta-Hexachlorocyclohexane

(CASRN 319-86-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DELTA-HEXACHLOROCYCLOHEXANE (CASRN 319-86-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

IRIS (U.S. EPA, 2008) does not report an RfD or RfC for delta-hexachlorocyclohexane (delta-HCH). The HEAST (U.S. EPA, 1997) states that data are inadequate for quantitative risk assessment for delta-HCH based on a Health and Environmental Effects Profile (HEEP) for hexachlorocyclohexanes (U.S. EPA, 1987). Delta-HCH is not included in the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006). The CARA list (U.S. EPA, 1991, 1994) includes only the previously mentioned HEEP (U.S. EPA, 1987). ATSDR (2005) developed a Toxicological Profile for alpha-, beta-, gamma-, and delta-HCH but did not derive oral or inhalation MRLs for delta-HCH. There is no Environmental Health Criteria Document available for delta-hexachlorocyclohexane (WHO, 2008). ACGIH (2007), OSHA (2007), and NIOSH (2008) have not established occupational health standards for delta-HCH.

On IRIS (U.S. EPA, 2008), delta-HCH is assigned to cancer Weight-of-Evidence Group D, "*Not Classifiable as to Human Carcinogenicity*," based on no available human data and inadequate animal data (verification date: 12/17/86). IARC (1987) did not assess the carcinogenicity of delta-HCH in its assessment of hexachlorocyclohexane isomers. Additionally, the carcinogenicity of delta-HCH has not been assessed by NTP (2005, 2008).

Delta hexachlorocyclohexane (DeltaHCH) is one of a series of isomers of the pesticide lindane. Lindane itself (Gamma hexachlorocyclohexane (GammaHCH)), or the technical grade mixture which is comprised approximately 8% of the delta isomer, has significantly more toxicity information available than the delta isomer. *In vivo* testing of DeltaHCH, a lipophilic neurodepressant agent has been largely inconclusive. *In vivo* results looked negative for cancer in rats (Ito, et al., 1973, 1975) and negative for bodyweight changes and body temperature changes (Camon, et al., 1988). *In vitro* studies in CHO cells showed some additivity between delta and gamma isomers. *In vitro* studies point two mechanisms of toxicity, although there is

cross-talk between the two pathways. The first appears to be related to the other HCH isomers well known interaction with the GABA receptor in neuronal tissue. Unlike the gamma isomer however, which is a GABA antagonist (like picrotoxin), delta is a partial allosteric agonist for the GABA receptor. While GammaHCH appears to bind near the picrotoxin site, DeltaHCH appears to involve (or overlap with) the binding site for barbiturates (Aspinwall et al 1997). Tissue specificity of the DeltaHCH response is explained by a lack of responsiveness to GABA receptors containing alpha 4, beta 1 or gamma 2L subunits. A chronic effects mechanism for carcinogenesis would appear to be related to its action on Ca signaling. The delta isomer has been repeatedly shown to cause the influx of calcium, and causing the activation of the protein kinase C pathway, and the activation of c-fos.

Literature searches were conducted from the 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for delta-HCH. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR DELTA-HEXACXHLOROCYCLOHEXANE

The data are inadequate to derive a p-RfD for delta-HCH. No dose-response information pertinent to any target organs is available in the current database; thus, the database lacks a study that could serve as a suitable basis for derivation of an RfD for delta-HCH.

FEASIBILITY OF DERIVING A PROVISIONAL RfC FOR DELTA-HEXACXHLOROCYCLOHEXANE

No inhalation toxicity data in humans or animals are identified; thus, no p-RfC could be derived for delta-HCH.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DELTA-HEXACXHLOROCYCLOHEXANE

Because of the lack of carcinogenic data in humans or animals, under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), this PPRTV document classifies delta-HCH as having "*Inadequate Information to Assess Carcinogenic Potential*."

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR OR INHALATION UNIT RISK FOR DELTA-HEXACXHLOROCYCLOHEXANE

Neither a p-OSF nor a p-IUR could be derived for delta-HCH because of the lack of suitable oral or inhalation in both humans and animals.

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